UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/073,881	05/06/98	RAO M	T4903.CIP

HM12/1003

JANE MASSEY LICATA, ESQ.
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON NJ 08053

EXAMINER	
KERR, J	
ART UNIT	**PAPER NUMBER**
1633	11

DATE MAILED: 10/03/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/073,881	Rao et al.
Examiner	**Group Art Unit**
Janet M. Kerr	1633

☒ Responsive to communication(s) filed on *Dec 9, 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-14* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-14* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-14 are being examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered vague and indefinite for the following reasons: it is unclear how neuroepithelial cells are induced to differentiate into neural crest stem cells as it there is no induction step recited in the method, the claim, as written, is incomplete; it is also unclear why there are two periods at the end of the claim.

Claim 2 is rendered vague and indefinite by the phrase "said inducing further comprises replating" as there is no initial plating recited in claim 1. The phrase lacks antecedent basis.

Claim 3 is rendered vague and indefinite for the following reasons: it is unclear what the first induction encompasses, and it is unclear how a mitogen can be withdrawn when there is no recitation of a mitogen in either claim 1 or claim 2.

Claim 5 is rendered vague and indefinite for the following reasons: it is unclear what the first induction encompasses, and it is unclear how chick embryo extract can be withdrawn when there is no recitation of chick embryo extract in either claim 1 or claim 2.

Claim 6 is rendered vague and indefinite by the phrase "wherein said inducing step comprises withdrawing a mitogen" as it is unclear how a mitogen can be withdrawn when there is no recitation of a mitogen in claim 1.

Claim 8 is rendered vague and indefinite by the phrase "wherein said inducing step comprises withdrawing chick embryo extract" it is unclear how chick embryo extract can be withdrawn when there is no recitation of chick embryo extract in either claim 1.

Claim 9 is rendered vague and indefinite by the phrase "dorsalizing agent" as it is unclear which agent is intended; it is also unclear what amount of a "dorsalizing agent" is required for the induction.

Claim 14 is rendered vague and indefinite by the phrases "inducing neuroepithelial stem cells to differentiate in vitro" and "inducing said neural crest stem cells to differentiate in vitro" as there are no induction steps recited in the claim. The claim, as written, is incomplete.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-3, 5, 6, 8 and 14 are rejected under 35 U.S.C. 102(a) as being anticipated by Rao *et al.* (Society for Neuroscience Abstracts, Vol. 22, Part 1, page 527, Abstract #215.12, 1996).

Rao *et al.* teach a method of generating neural crest stem cells comprising culturing neuroepithelial stem cells in the presence of FGF and chick embryo extract (CEE), and inducing neuroepithelial stem cells to differentiate *in vitro*, thereby generating said neural crest stem cells.

Rao *et al.* teach that cultured and passaged NEP cells can differentiate into neurons and oligodendrocytes, as well as ChAT and p75 immunoreactive cells, which are likely to be motoneurons, i.e., cells of the peripheral nervous system, when plated on laminin in the absence of CEE (i.e., withdrawal of a mitogen). As the NEP cells differentiate into neural crest stem cell derivatives, the method of Rao *et al.* necessarily produces neural crest stem cells from NEP cells barring evidence to the contrary.

As the reference of Rao *et al.* teach all of the limitations of the claims, the reference anticipates the claimed invention.

Claims 1, 2, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Ray *et al.*, (J. Neuroscience, 14:3548-3564, 1994).

Ray *et al.* teach a method for generating mammalian neural crest cells comprising inducing neuroepithelial stem cells to differentiate *in vitro*, thereby generating neural crest stem cells. The method of inducing comprises replating neuroepithelial stem cells on a laminin-coated substrate (see, e.g., page 3550, left column, under "Cell Culture"). As the induction results in a population of LNGFR-positive/Chat-positive cells, which are identified as motoneurons (see, e.g., page 3557, left column, first full paragraph), the method steps of Ray *et al.* necessarily result in the differentiation of neural crest stem cells from neuroepithelial cells and differentiation of peripheral nervous system cells from the neural crest stem cells, barring evidence to the contrary. Thus, the teachings of Ray *et al.* anticipate the claimed invention.

Claims 1, 6-8, and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Anderson *et al.* (U.S. Patent No. 5,589,376, 12/31/96, effective filing date of 7/27/92).

Anderson *et al.* teach a method for generating mammalian neural crest stem cells comprising inducing neuroepithelial stem cells to differentiate *in vitro*, thereby generating the neural crest stem cells. The method comprises culturing neural tubes (which inherently comprise neuroepithelial cells) onto fibronectin-coated plates and isolating the neural crest cells which

migrate onto the fibronectin substrate. The neural crest cells are further cultured in the presence of basal medium supplemented with 10% chick embryo extract and FGF and can be differentiated to peripheral nervous system cells by changing the medium comprising chick embryo extract to medium comprising fetal calf serum and forskolin (see, e.g., Examples 1-4 and claims 1-10), i.e., removing the mitogens FGF, and chick embryo extract. As the neural tube necessarily comprises neuroepithelial stem cells which are differentiated into neural crest stem cells by removing mitogens from the medium, the reference of Anderson *et al.* anticipates the claimed invention.

Claims 1, 6-8, and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Anderson *et al.* (U.S. Patent No. 5,824,489, 1998, effective filing date of October, 29, 1992).

Anderson *et al.* teach a method for generating mammalian neural crest stem cells comprising inducing neuroepithelial stem cells to differentiate *in vitro*, thereby generating the neural crest stem cells. The method comprises culturing neural tubes (which inherently comprise neuroepithelial cells) onto fibronectin-coated plates and isolating the neural crest cells which migrate onto the fibronectin substrate. The neural crest cells are further cultured in the presence of basal medium supplemented with 10% chick embryo extract and FGF (see, e.g., Examples 1-3 and claims 1-21). Anderson *et al.* also teach differentiating the neural crest cells to peripheral nervous system cells by changing the medium comprising chick embryo extract to medium comprising fetal calf serum and forskolin (see, e.g., Example 4 and claims 10-21), i.e., removing the mitogens FGF, and chick embryo extract. As the neural tube necessarily comprises neuroepithelial stem cells which are differentiated into neural crest stem cells by removing mitogens from the medium, the reference of Anderson *et al.* anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4, 7, and 9-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rao *et al.* (Society for Neuroscience Abstracts, Vol. 22, Part 1, page 527, Abstract #215.12, 1996), taken with Varley *et al.* (Experimental Neurology, 140:84-94, 1996).

Rao *et al.* teach a method of generating neural crest stem cells comprising culturing neuroepithelial stem cells in the presence of FGF and chick embryo extract (CEE), and inducing neuroepithelial stem cells to differentiate *in vitro*, thereby generating said neural crest stem cells. Rao *et al.* teach that cultured and passaged NEP cells can differentiate into neurons and oligodendrocytes when plated on laminin in the absence of CEE (i.e., withdrawal of a mitogen), as well as ChAT and p75 immunoreactive cells, which are likely to be motoneurons, i.e., cells of the peripheral nervous system.

Rao *et al.* do not teach the removal of FGF from the medium, or addition of a dorsalizing agent such as the bone morphogenetic proteins BMP-2, BMP-4, or BMP-7. However, Varley *et al.* teach obtaining cultures of neural crest cells from explantation of quail embryos and culturing the neural crest cells in the presence of recombinant BMP-2 and BMP-4 (see, e.g., page 85, under "Materials and Methods"). The cells were grown in medium comprising chick embryo extract, which allow the neural crest cells to develop to a point where they are responsive to the BMPs (see, e.g., page 86, right column, second full paragraph). Varley *et al.* also teach that selected

members of the BMP family, e.g., BMP-2, BMP-4, and BMP-7, play several important roles in establishing neural crest cell identity and promoting subsequent differentiation along specific phenotypic pathways (see, e.g., page 85, left column, first full paragraph, page 89, under "Discussion", page 91, under "Function and Sequence Homology of the BMPs", and page 92, right column, second full paragraph). With regard to removal of the FGF from the medium, in view of the teachings of Rao *et al.* that FGF is a mitogen which allows proliferation and the maintenance of the undifferentiated phenotype of NEP cells, it would have been obvious to withdraw FGF to allow differentiation of the NEP cells into neural crest cells.

It would have been obvious for one of ordinary skill in the art at the time the claimed invention was made to modify the cell culture of Rao *et al.* by including a dorsalizing agent such as BMP-2, BMP-4, or BMP-7 in the cell culture medium in view of the teachings of Varley *et al.* that BMP-2, BMP-4, or BMP-7 play a role in establishing neural crest cell identity and in promoting subsequent differentiation along specific phenotypic pathways. Thus, one of ordinary skill in the art would have been motivated to include the claimed BMPs during the culturing of neural crest precursor cells to induce the differentiation of these cells into neural crest cells. Alternatively, one of skill in the art would have been motivated to remove a mitogen from the cell culture medium to allow the cells to differentiate into neural crest cells. In addition, one of ordinary skill in the art would have had a high expectation of inducing neural crest cell development in the cell culture method of Rao *et al.* by adding the BMPs taught by Varley *et al.* to the NEP cultures, or removing the FGF of Rao *et al.* from the NEP cultures, barring evidence to the contrary.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Claims 9-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ray *et al.*, (J. Neuroscience, 14:3548-3564, 1994) taken with Varley *et al.* (Experimental Neurology, 140:84-94, 1996).

Ray *et al.* teach a method for generating mammalian neural crest cells comprising inducing neuroepithelial stem cells to differentiate *in vitro*, thereby generating neural crest stem cells. The method of inducing comprises replating neuroepithelial stem cells on a laminin-coated substrate (see, e.g., page 3550, left column, under "Cell Culture"). As the induction results in a population of LNGFR-positive/ChAT-positive cells, which are identified as motoneurons (see, e.g., page 3557, left column, first full paragraph), the method steps of Ray *et al.* necessarily result in the differentiation of neural crest stem cells from neuroepithelial cells and differentiation of peripheral nervous system cells from the neural crest stem cells, barring evidence to the contrary.

Ray *et al.* do not teach the addition of a dorsalizing agent such as the bone morphogenetic proteins BMP-2, BMP-4, or BMP-7. However, Varley *et al.* teach obtaining cultures of neural crest cells from explantation of quail embryos and culturing the neural crest cells in the presence of recombinant BMP-2 and BMP-4 (see, e.g., page 85, under "Materials and Methods"). The cells were grown in medium comprising chick embryo extract, which allow the neural crest cells to develop to a point where they are responsive to the BMPs (see, e.g., page 86, right column, second full paragraph). Varley *et al.* also teach that selected members of the BMP family, e.g., BMP-2, BMP-4, and BMP-7, play several important roles in establishing neural crest cell identity and promoting subsequent differentiation along specific phenotypic pathways (see, e.g., page 85, left column, first full paragraph, page 89, under "Discussion", page 91, under "Function and Sequence Homology of the BMPs", and page 92, right column, second full paragraph).

It would have been obvious for one of ordinary skill in the art at the time the claimed invention was made to modify the cell culture of Ray *et al.* by including a dorsalizing agent such as BMP-2, BMP-4, or BMP-7 in the cell culture medium in view of the teachings of Varley *et al.* that BMP-2, BMP-4, or BMP-7 play a role in establishing neural crest cell identity and in promoting subsequent differentiation along specific phenotypic pathways. Thus, one of ordinary

skill in the art would have been motivated to include the claimed BMPs during the culturing of neural crest precursor cells to induce the differentiation of these cells into neural crest cells. In addition, one of ordinary skill in the art would have had a high expectation of inducing neural crest cell development in the cell culture method of Ray *et al.* by adding the BMPs taught by Varley *et al.* to the cultures barring evidence to the contrary.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Claims 9-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson *et al.* (U.S. Patent No. 5,589,376, 12/31/96, effective filing date of 7/27/92), or alternatively, over Anderson *et al.* (U.S. Patent No. 5,824,489, 1998, effective filing date of October, 29, 1992), either reference taken with Varley *et al.* (Experimental Neurology, 140:84-94, 1996).

Anderson *et al.* (U.S. Patent No. 5,589,376) teach a method for generating mammalian neural crest stem cells comprising inducing neuroepithelial stem cells to differentiate *in vitro*, thereby generating the neural crest stem cells. The method comprises culturing neural tubes (which inherently comprise neuroepithelial cells) onto fibronectin-coated plates and isolating the neural crest cells which migrate onto the fibronectin substrate. The neural crest cells are further cultured in the presence of basal medium supplemented with 10% chick embryo extract and FGF and can be differentiated to peripheral nervous system cells by changing the medium comprising chick embryo extract to medium comprising fetal calf serum and forskolin (see, e.g., Examples 1-4 and claims 1-10), i.e., removing the mitogens FGF, and chick embryo extract.

Alternatively, Anderson *et al.* (U.S. Patent No. 5,824,489) teach a method for generating mammalian neural crest stem cells comprising inducing neuroepithelial stem cells to differentiate *in vitro*, thereby generating the neural crest stem cells. The method comprises culturing neural tubes (which inherently comprise neuroepithelial cells) onto fibronectin-coated plates and isolating the neural crest cells which migrate onto the fibronectin substrate. The neural crest cells are

further cultured in the presence of basal medium supplemented with 10% chick embryo extract (see, e.g., Examples 1-3 and claims 1-21). Anderson *et al.* also teach differentiating the neural crest cells to peripheral nervous system cells comprising removing the chick embryo extract, i.e., a mitogen from the culture medium (see, e.g., Example 4 and claims 10-21). The neural tube necessarily comprises neuroepithelial stem cells which are differentiated into neural crest stem cells by removing mitogens from the medium, barring evidence to the contrary.

Anderson *et al.* (either reference) do not teach the addition of a dorsalizing agent such as the bone morphogenetic proteins BMP-2, BMP-4, or BMP-7. However, Varley *et al.* teach obtaining cultures of neural crest cells from explantation of quail embryos and culturing the neural crest cells in the presence of recombinant BMP-2 and BMP-4 (see, e.g., page 85, under "Materials and Methods"). The cells were grown in medium comprising chick embryo extract, which allow the neural crest cells to develop to a point where they are responsive to the BMPs (see, e.g., page 86, right column, second full paragraph). Varley *et al.* also teach that selected members of the BMP family, e.g., BMP-2, BMP-4, and BMP-7, play several important roles in establishing neural crest cell identity and promoting subsequent differentiation along specific phenotypic pathways (see, e.g., page 85, left column, first full paragraph, page 89, under "Discussion", page 91, under "Function and Sequence Homology of the BMPs", and page 92, right column, second full paragraph).

It would have been obvious for one of ordinary skill in the art at the time the claimed invention was made to modify the cell culture of Anderson *et al.* (either reference) by including a dorsalizing agent such as BMP-2, BMP-4, or BMP-7 in the cell culture medium in view of the teachings of Varley *et al.* that BMP-2, BMP-4, or BMP-7 play a role in establishing neural crest cell identity and in promoting subsequent differentiation along specific phenotypic pathways. Thus, one of ordinary skill in the art would have been motivated to include the claimed BMPs during the culturing of neural crest precursor cells to induce the differentiation of these cells into neural crest cells. One of ordinary skill in the art would have had a high expectation of inducing

neural crest cell development in the cell culture method of Anderson *et al.* (either reference) by adding the BMPs taught by Varley *et al.* to the cultures barring evidence to the contrary.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to John LeGuyader, Supervisory Primary Examiner of Art Unit 1633, at (703) 308-0447. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633.

Janet M. Kerr, Ph.D.
Patent Examiner
Group 1600

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600